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REVIEW ARTICLE

Lower Limb Oedema Following Distal Arterial Bypass Grafting

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Lower-limb oedema following arterial bypass surgery for ischemia is a common sequela which can complicate wound healing or delay resumption of mobility. Its exact pathogenesis remains uncertain but many theories have been proposed. Lymphatic disruption during arterial exposure, and endothelial damage from atrophy of the media and oxygen-derived free radical release are currently favoured hypotheses Infrequently, deep vein thrombosis follows surgery and may exacerbate the condition. Efforts aimed at reducing the oedema, such as the use of lymphatic preserving incisional approaches or the use of antioxidants, have given conflicting results. The use of compression hosiery and leg elevation appear to be the most effective measures in reducing postoperative lower limb oedema

Introduction

Intermittent claudication affects 5–10% of the population over 65 years of age, and a significant proportion of these individuals will require surgical or interventional radiological procedures to alleviate incapacitating claudication or critical ischaemia.[1] This makes lower-limb bypass surgery one of the most commonly performed vascular procedures in affluent societies. Unfortunately these procedures can be associated with significant morbidity, one of which is post-revascularisation lower-limb oedema. This complication has been reported in up to 100% of patients undergoing femoropopliteal bypass grafting and, although usually mild, may lead to an increase of as much as 30% in initial limb volume (Table 1). In addition to causing undue anxiety, it may delay ambulation and compromise healing in patients with associated ischaemic ulcers or in those who require distal amputation. The use of compression stockings in the elderly may necessitate extra supervision and contribute towards prolonging inpatient hospital stay and a higher cost to the National Health Service. The control of dependency swelling has been found to be important in minimising wound complications following pedal bypass.[2] Rarely, the oedema may be severe enough to cause compartment syndrome of a degree which makes fasciotomy obligatory, but this measure is fortunately only necessary in less than 0.5% of all cases of elective arterial reconstruction.[3,4]

Table 1. The incidence of lower limb oedema following distal arterial bypass surgery for ischaemia.

Authors	Incidence of oedema (%)
Hamer[8]	95
Eickhoff and Engell[10]	100
Herreros *et al* [12]	93
Hannequin *et al.*[13]	48
Porter *et al* [15]	64
Abu-Rahman *et al.*[17]	40
Campbell *et al* [27]	85

Despite the frequency with which postoperative oedema occurs, its aetiology and the manner in which excess fluid is distributed in the various compartments of the limb remain controversial and incompletely understood. Melberg *et al.*[5] demonstrated significant elevation in intramuscular pressure 2 days after surgery, reaching levels twice that of the initial pressure, then gradually decreasing but still elevated even by the sixth postoperative day. This rise in intramuscular pressure was unrelated to the severity of preoperative ischaemia or length of surgery. In patients whose reconstructive arterial surgery was unsuccessful, intramuscular pressure and calf circumference remained unchanged postoperatively. More recent evidence of oedema mainly confined to the subcutaneous tissue,

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however, refutes earlier findings of intramuscular pressure elevation. Using computer tomography and magnetic resonance imaging, an increase in volume of up to 40% has been shown to occur in the subcutaneous tissue with little change observed in the muscle compartments.[6,7] This observation, despite previous suggestions, is supported by the lack of elevation in interstitial fluid pressure in the muscle compartments compared to that in the subcutaneous tissue, the latter rising by more than 10%.

Even more controversial is the precise cause of the increase in limb volume. It is becoming clearer that many conducive factors are likely to be responsible, different elements contributing to a varying degree in each individual patient. The diversity of these aetiological factors has meant that prevention and treatment of oedema has proved elusive. Until the contribution made by each of those factors has been clarified, a simple therapeutic strategy is precluded.

Deep vein thrombosis

Deep vein thrombosis is not a common occurrence following femoropopliteal bypass grafting but may exacerbate the oedema when present. The incidence of deep vein thrombosis, in this cohort of patients, varies from series to series and ranges from 0–40% (Table 2). In one study,[8] thrombosis of the major deep veins was demonstrated to be common in those whose lower limb circumference increased by more than 4.5 cm; no patient whose leg swelling was less than 1.5 cm had associated deep vein thrombosis, while all those whose legs showed a circumferential increase exceeding 4.5 cm were found to have thrombosis of the deep veins. This report also showed that vein thrombosis was more prevalent in patients undergoing below-knee bypass, particularly in those with critical ischaemia. Others have not substantiated these findings, and the incidence of deep vein thrombosis is found to be much less than the number of patients developing significant oedema (Table 2). This discrepancy would suggest that other aetiological factors are of greater importance, even though the presence of thrombosed deep veins may be a compounding factor in some.

Table 2. The incidence of deep venous thrombosis following femoropopliteal bypass grafting.

Authors	Incidence of DVT (%)	Diagnostic technique
Hamer[8]	41	Phlebography
Herreros *et al* [12]	7	Phlebography
Porter *et al* [15]	0	Phlebography
Abu-Rahman *et al* [17]	8	Phlebography
Myhre *et al*.[19]	8	Phebography
Storen *et al* [20]	7	Phlebography
Husni[23]	9	Phlebography
Farkas *et al* [58]	3	Duplex/phlebography

Lymphatic disruption

On the evidence available from many studies, the most important aetiological factor contributing to swelling following lower-limb bypass grafting is lymphatic. The lymphatic drainage of the leg converges at the inguinal region via channels, most of which are distributed anterior to the femoral vessels along with some lateral and medial extensions. Numerous lymphatics also surround the neurovascular bundle in the popliteal fossa. Both these sets of lymphatic channels communicate with neighbouring veins.[9] Dissection in the groin and popliteal region is accompanied by significant disruption of these lymphatic channels and their venous communications quite independently of the outcome of surgery.[10] A bypass procedure, therefore, is not a prerequisite to postoperative oedema, as even simple exploration may lead to its development.[11] It has been observed that patients undergoing prophylactic reconstruction without ischaemia for popliteal aneurysm developed the same degree of limb oedema as those whose operation was performed for critical limb ischaemia, and that the degree of swelling is proportionate to the level of bypass, viz. minimally following suprainguinal and maximally after below-knee bypass surgery.[11,12] In addition, the use of autologous vein graft, the harvesting of which requires extensive dissection, is associated with much more swelling than when a prosthetic graft is used.

Using lymphoscintigraphy, postoperative morphological changes in those who developed oedema differed markedly from those who did not, even though no significant difference was observed in the rate of lymph flow.[13] This evidence concurs with the finding that propulsion of lymph remains intact and that the defect in lymph transport is secondary to lymph vessel disruption.[14] It has also been observed that the duration and severity of the lower limb oedema correlates with the magnitude of lymphatic disruption.[15] The number of superficial lymphatic channels may be reduced four-fold following femoropopliteal bypass surgery and the degree of oedema has been found to be inversely proportional to the number of remaining intact lymphatic channels.[16]

Porter *et al.*[15] showed clearly that postoperative swelling may be averted by minimising damage to lymphatics. In their study, patients underwent a femoropopliteal bypass either through a conventional or a lymphatic sparing groin dissection: six out of eight patients who had a conventional groin approach developed swelling, whereas only three out of six did so when the approach was modified to preserve the lymphatics.

More recently, Abu Rahman *et al.*[17] noted that lymphatic sparing femoral and popliteal dissection resulted in much lower degrees of oedema than when conventional exposures of these respective arteries were employed. In a more extensive study, they randomised patients into four groups: the first had lymphatic conserving inguinal and conventional popliteal dissection, the second a lymphatic sparing popliteal but conventional inguinal dissection, the third lymphatic preserving inguinal and popliteal dissections, and the fourth had conventional approaches to both inguinal and popliteal regions. Oedema was observed to be highest in the fourth group of patients.

The inference that lymphatic disruption is the major cause of lower limb oedema following infrainguinal bypass grafting is by no means irrefutable as contradictory evidence could be cited. Firstly, in the study by Porter *et al.*,[15] regardless of lymphatic sparing dissections 50% of patients developed swelling, perhaps because preservation of lymphatic channels in the popliteal fossa, found beneficial by some, had not been achieved.[17,18] Secondly, leakage of lymph from interrupted lymph channels observed in those who suffered postoperative oedema can also occur in those who do not develop oedema.[19] Storen *et al.*[20] found no difference in the extent of lymphatic disruption between patients who developed oedema and those, with no increase in limb circumference; in addition pronounced oedema was present in those patients with normal lymphangiograms and venograms. Thirdly, Fernandez *et al.*[21] demonstrated increased lymph flow in the superficial lymphatics, inferring that in some patients the post-reconstructive oedema may not be due to lymphatic disruption. Finally, the lesser degree of swelling observed in those whose bypass failed simply implies that factors dependent on a successful revascularisation are important.

Increased capillary filtration

It has been shown that chronic arterial insufficiency leads to medial atrophy, which may result in overstretching, fragmentation and rupture of the vessel wall during revascularisation.[22,23] The associated hyperaemia consequent upon reperfusion of an ischaemic limb may be a predictive indicator of oedema which manifests itself with ambulation; the severity and duration of oedema parallels that of hyperaemia. This hyperaemic response affected mainly those whose bypass surgery was successful and lasted from 6 to 60 days.[24] Pitting oedema was present only in those whose hyperaemia lasted more than a week after surgery, while none of those with immediate failure of the reconstruction developed hyperaemia or oedema even though dissection to expose the arteries would have damaged the major lymphatic channels. Hyperaemic distension of the limb vasculature as a result of an increased head of pressure and decreased resistance may account for the initial increase in limb volume prior to ambulation. It may also explain the relative increase in limb volume which follows percutaneous transfemoral angioplasty for lower limb ischaemia.[25] This loss of vascular tone may lead to a rise in the capillary filtration coefficient, a measure of capillary permeability at a given pressure.[26] Another factor thought to contribute to the increase in capillary filtration is the elevation in hydrostatic pressure due to failure of the venous pump during ambulation, the latter considered to be due to chronic ischaemic skeletal muscle dystrophy.[8]

The increase in capillary permeability and filtration permits leakage of macromolecules into the interstitial space. Using I^{125} labelled albumin, Campbell *et al.*[27] demonstrated a three-fold increase in albumin concentration in the operated leg compared to the contralateral leg. The accumulation of albumin was found to occur in the entire leg, including the muscular compartment. Samples obtained of subcutaneous interstitial fluid using the blister suction technique demonstrated an increase in α2-macroglobulin and immunoglobulin G.[28] This sequestration of macromolecules in the limb was accompanied by a fall in plasma protein and albumin concentrations sustained for at least 10 days postoperatively. Although this increase in capillary filtration has been attributed to smooth muscle atrophy and mechanical disruption of the capillary consequent upon increased flow, there is evidence to suggest that the generation of oxygen-derived free radicals can damage the vascular endothelium.[22,29–31]

Oxygen-derived free radicals

It is now well established that restoration of blood flow to ischaemic tissues can lead to complications, at

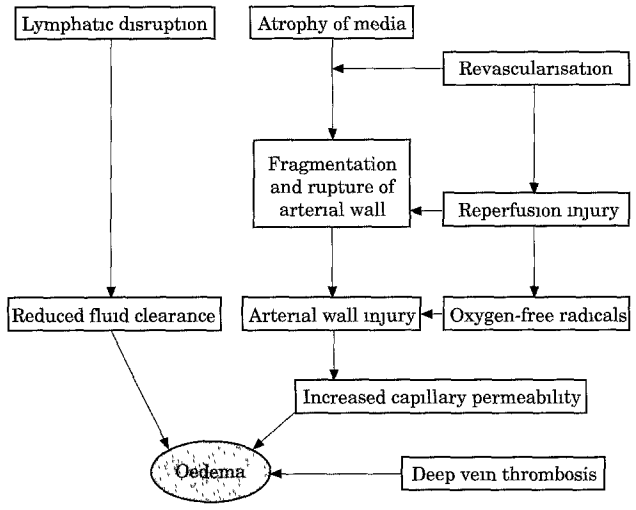

Fig. 1. The possible aetiological factors of lower limb oedema following arterial bypass grafting.

best local damage, at worst injury to multiple remote organs provoked by the generation of oxygen-derived free radicals during reperfusion.[32–34] These free radicals are cytotoxic species which injure cells through processes such as lipid peroxidation which damage the cell membrane via a series of reactions.[30] Normally this free radical induced injury is limited *in vivo* by antioxidants such as ascorbic acid (vitamin C) and the major lipid phase, α-tocopherol (vitamin E), which is incorporated in the cellular membrane. It has been suggested that the major source of oxygen-derived free radicals following ischaemia-reperfusion injury is the xanthine oxidase pathway.[35] This enzyme occurs naturally as the xanthine dehydrogenase and is found in abundance in the brain, heart, intestine and skeletal muscles. The dehydrogenase form catalyses the reaction which converts xanthine and water to uric acid and a proton with reduction of the nicotinamide dinucleotide molecule. During ischaemia the dehydrogenase form is converted by a calcium dependent proteolytic enzyme to xanthine oxidase which generates uric acid and superoxide anion from hypoxanthine and oxygen. Together with the accumulation of hypoxanthine from the catabolism of adenosine triphosphate during ischemia, conditions favour the generation of oxygen-derived free radicals in response to the surge of oxygen concentration during reperfusion. Support for this chain of events is the ability of allopurinol (a xanthine oxidase inhibitor) and mannitol (a hydroxyl radical scavenger) to reduce the tissue damage following revascularisation.[31,34,36]

In addition to the production of oxygen-derived radicals, the calcium paradox can activate phospholipase A2 releasing arachidonic acid as well as the complement cascade.[37] Arachidonic acid is then converted to thromboxanes or leucotrienes depending on whether it follows the cycloxygenase or lipoxygenase pathways. Some of these arachidonic acid metabolites and breakdown products of complements are potent chemoattractants which can stimulate neutrophils and up-regulate adhesive molecules on the endothelial membrane.[32,38,39] A consequence of this is the margination and adhesion of neutrophils along the wall of the vessel leading to release of more oxygen-derived free radicals and other proteolytic enzymes further damaging the endothelium. In addition, the accumulation of neutrophils in the capilllaries may cause sludging and reduction of blood flow, namely the "no reflow" phenomenon.[40]

Cytokines may also be released from reperfused ischaemic skeletal muscle, as has been demonstrated in the isolated leg, which led to a rise in tumour necrosis factor, interleukin(IL)-1 and IL-6.[41–43] This is supported by the finding in the venous effluent of gracilis muscle rendered ischaemic of thromboxane A2 and IL-1 in concentrations which were significantly higher than those noted systemically.[43] The production of these cytokines may be related to the generation of oxygen-derived free radicals by endothelial cells and may be attenuated by pretreatment with superoxide dismutase and glutathione peroxidase.[44] In addition to causing local damage to the revascularised limb, spillage of these agents into the systemic circulation may have deleterious effects on remote organs.[32]

In skeletal muscles the fall in transmembrane potential difference was worse during reperfusion when compared to that in ischaemia alone.[45] Although Persson *et al.*[46] were not able to show a rise in the concentration of malondialdehyde in reperfused ischaemic muscle following arterial bypass surgery, they demonstrated its increase with iron stimulation, suggesting a greater susceptibility to free radical induced lipid peroxidation. However, by serially measuring the concentration of malondialdehyde, an elevation was observed during revascularisation following femoropopliteal bypass grafting.[33] This was accompanied by a fall in the concentration of vitamin E, suggesting its consumption by free radicals. In addition, the peak malondialdehyde rise and maximum fall in antioxidant was found to be significant only in those who subsequently developed lower-limb oedema. The finding that lipid peroxidation was significant only in patients whose bypass was successful may explain their greater degree of post-operative limb swelling compared to those whose revascularisation was not optimal.[47] Corollary studies showed that by using allopurinol or a cocktail of

vitamin A, vitamin C and vitamin E to minimise the generation of oxygen-derived free radicals lower-limb swelling can be significantly reduced.[34,48] The fact that the increase in leg volume is confined to subcutaneous tissue may be attributable to its rich store of poly-unsaturated fatty acids, which would be vulnerable to lipid peroxidation.

The more recent discovery that percutaneous transfemoral angioplasty is associated with some swelling would support the free radical theory of causation, particularly as lymphatic-channels are not disrupted by this procedure.[25] No attempt has been made so far to determine whether the degree of swelling which follows suprainguinal and infrainguinal angioplasties is the same or not. It may be argued that oedema found in patients undergoing radiological revascularisation is due to hyperaemic distension of the vascular network secondary to loss of vascular tone, but this does not explain the delayed increase in limb volume.[25]

Treatment

Unfortunately many questions regarding the oedema which follows lower limb bypass grafting for ischaemia remain unexplained. There is no doubt that the condition has a multifactorial pathogenesis, each factor being of varying importance depending on the circumstances in each case (Fig. 1). Lymphatic disruption, increased capillary filtration and ischaemia-reperfusion injury are possible common contributory factors, and in a mere handful the development of deep vein thrombosis will exacerbate the problem. It is precisely the lack of understanding of the exact aetiology which accounts for the absence of a therapeutic protocol either to treat or to prevent the complication.

Antioxidants have been used successfully by some, but widespread acceptance of such recommendations tends to be poor and often viewed with scepticism. Preadministration of allopurinol has been shown to reduce lower limb oedema: in a randomised controlled study, patients receiving allopurinol were found to develop an almost 50% reduction in swelling compared to a placebo group.[34] Although allopurinol limits lower limb swelling, its mode of action is still not entirely clear. It has been suggested that it acts by inhibiting xanthine oxidase activity, while others propose that its beneficial effect may be related to its more active metabolite, oxypurinol, which is a scavenger of hydroxyl radicals.[49–51] The process of conversion of allopurinal to oxypurinol takes at least 12 h, a fact which explains the failure of allopurinol to show any beneficial effect when used shortly before the ischaemia-reperfusion insult. It is also felt that the protective effect of oxypurinol may not be sustained beyond 6 h of reperfusion and that short-term administration may only delay rather than prevent tissue damage after reperfusion. Perler *et al.*,[52] however, demonstrated that both allopurinol and oxypurinol are effective in preventing the development of compartment syndrome following 6 h to 12 h of hind-limb ischaemia.

A cocktail of antioxidants containing alpha-tocopherol, ascorbic acid and retinol may reduce oxidative damage found in patients undergoing lower limb revascularisation procedures.[48] Intravenous administration of the concoction prior to the start of reperfusion prevented the postoperative elevation of plasma concentration of malondialdehyde and lower-limb swelling observed in patients who were not given the mixture of antioxidants. Unfortunately, this study[48] consisted of a heterogenous group of patients suffering both acute and chronic ischaemia of the lower and upper limbs. Mannitol, another hydroxyl radical scavenger, has also been found to be effective in abrogating oedema after embolectomy. In a study conducted by Buchbinder *et al.*,[53] 15 consecutive patients undergoing emergency vascular revascularisation for critical limb ischaemia were given 20% mannitol intravenously just prior to the re-establishment of blood flow, followed by an infusion for up to 24 h thereafter: none of these patients suffered compartment syndrome or required fasciotomy, leading to the inference that mannitol exerted a protective influence in ischaemia-reperfusion injury of skeletal muscle. Nevertheless, this was not a randomised controlled study and therefore any conclusions drawn from the results must be viewed with caution. In addition, Persson *et al.*[54] were unable to demonstrate any advantage in using mannitol in a very small group of patients undergoing lower-limb bypass surgery, but once again criticisms with regard to the lack of randomisation are equally applicable to this study. Many other antioxidants have been found to be effective in reducing cellular damage following ischaemia-reperfusion injury, but their role in this cohort of patients remains undetermined.[31]

Iloprost, a prostacyclin analogue, has been shown to minimise capillary endothelial swelling following femorodistal reconstruction.[55] Capillary damage with endothelial swelling was shown to be a generalised phenomenon not localised to the region of reperfusion and may be precipitated by the systemic release of vasoactive agents following revascularisation; in this

randomised controlled clinical study, they found that this endothelial swelling may be limited by treatment with iloprost.

The benefit of lymphatic sparing approaches to the femoral and popliteal arteries aimed at reducing lower-limb oedema has not been demonstrated consistently. In a prospective randomised study, Haaverstad *et al.*[56] were unable to show that swelling in patients undergoing lower-limb reconstruction surgery using lymphatic preserving groin incision was lower than in those subjected to a conventional approach.

Conclusion

In view of the multiplicity of contributing factors, optimal prevention of oedema following lower-limb arterial bypass surgery may be achieved only by applying a combination of therapeutic regimens. Dissection carried out using the lymphatic sparing approach, preadministration of an antioxidant as well as prophylaxis against deep vein thrombosis could all be recommended. Further studies, however, are necessary in order to examine more clearly the role of each of these contributory factors in the development of lower-limb oedema before sound and effective therapy can be implemented. It is worth quoting Bone[57] in his comment on the Systemic Inflammatory Response Syndrome (SIRS), "... spend more time on achieving an accurate diagnosis and less time searching for a magic bullet". Therefore, at this point in time, leg elevation and compression stockings may represent the most effective measures available until a more definitive therapeutic regimen is clearly established.[2,53]

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